



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-D-1213]

Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a guidance for industry entitled "Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity." It is intended to help sponsors of such drugs determine whether they should submit environmental assessments (EA) for drug applications and certain supplements, and to clarify what information such sponsors should include if they submit a claim of categorical exclusion instead of an EA.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may

not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2015-D-1213 for Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Raanan A. Bloom, Environmental Assessment Team, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-2185, CDER.EA.Team@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

## I. Background

FDA is announcing the availability of a guidance for industry entitled "Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity." This guidance finalizes the draft of the same name that published on April 29, 2015. The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions and to ensure that the interested and affected public is informed of the environmental analyses. FDA regulations at 21 CFR part 25 specify that EAs must be submitted as part of certain new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologic license applications (BLAs), supplements to such applications, and investigational new drug applications (INDs), and for various other actions, unless the action qualifies for a categorical exclusion. Failure to submit either an EA or a claim of categorical exclusion is sufficient grounds for FDA to refuse to file or approve an application (21 CFR 25.15(a), 314.101(d)(4) and 601.2(a) and (c)).

Categorical exclusions for actions related to human drugs and biologics are listed at 21 CFR 25.31. This guidance focuses on the categorical exclusion for actions on NDAs and NDA supplements that would increase the use of an active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment would be below 1 part per billion (1 ppb) (21 CFR 25.31(b)). Although an action that qualifies for this exclusion ordinarily does not require an EA, FDA will require “at least an EA” if “extraordinary circumstances” indicate that the specific proposed action (e.g., the approval of the NDA) may significantly affect the quality of the human environment (21 CFR 25.21). Research indicates that drugs with endocrine-related activity and, more specifically, drugs with Estrogenic, Androgenic, or Thyroid Activity (E, A, or T) activity have the potential to cause developmental or reproductive effects when present in the aquatic environment at concentrations below 1 ppb.<sup>1</sup>

FDA has, on a case-by-case basis, requested additional information from sponsors of NDAs and NDA supplements for drugs with E, A, or T activity to help it determine whether extraordinary circumstances exist. However, late cycle requests for additional environmental information have the potential to delay approval of applications. Accordingly, this guidance is intended to clarify that sponsors of drugs with potential E, A, or T activity should consult with the Agency early in product development concerning the information FDA may need to determine whether an EA will be required or whether a claim of categorical exclusion will be acceptable, and what information should be included in the EA or claim of categorical exclusion.

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<sup>1</sup> For example, see Section II.C (pp. 7-13) of USFDA, 2013, “Response to Citizen Petition to the FDA Commissioner under the National Environmental Policy Act and Administrative Procedure Act Requesting an Amendment to an FDA Rule Regarding Human Drugs and Biologics,” Docket No. FDA-2010-P-0377; U.S. Environmental Protection Agency (USEPA), Endocrine Disruptor Screening Program (EDSP), last accessed February 17, 2015, at <http://www.epa.gov/endo>; and Organisation for Economic Co-operation and Development (OECD), OECD Work Related to Endocrine Disruptors, last accessed February 17, 2015, at <http://www.oecd.org/env/ehs/testing/oecdworkrelatedtoendocrinedisrupters.htm>.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

## II. The Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 25 have been approved under OMB control number 0910-0322 and the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001.

## III. Electronic Access

Persons with access to the Internet may obtain the guidance at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: March 1, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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